PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Peter D. DAVIS
Serial No.: 10/049,248 Group No.: 1626
Filed: May 6, 2002 Examiner.: Rebecca L. Anderson
For: STILBENES WITH VASCULAR DAMAGING ACTIVITY

Attorney Docket No.: U013864-1

Commissioner for Patents
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DECLARATION UNDER 37 CFR 1.132

I, Peter David Davis, hereby declare:

1. I am the inventor of the invention described and claimed in US application serial no. 10/049,248 ("the application").. My curricum vitae is annexed hereto as Exhibit 1.

2. I have had experimentation conducted to test the activity of the compound of Example 2 described at pages 12-13 of the application. The experimentation, which is described below, was conducted under my supervision and I have first hand knowledge of the experimentation and results.

3. **Enhanced Activity of Novel VTAs Against CA4P-resistant Tumours**

The round-cell sarcoma, SaS, grown as a syngeneic subcutaneous tumour in CBA mice, is highly resistant to combretastatin A4 phosphate (Parkins CS, Holder AL, Hill SA, *et al.*, Determinants of anti-vascular action by combretastatin A-4 phosphate: role of nitric oxide. *Brit J Cancer* 2000; 83: 811-816 and Davis et al. Enhancement of vascular targeting by inhibitors of nitric oxide synthase. *Int J Radiat Oncol Biol Phys.* 2002; 54:1532-6). The following experiments show the surprising activity of the compound of Example 2 ((Z)-2-methyl-5-[2-(3,4,5-trimethoxyphenyl)ethenyl]phenyl dihydrogen phosphate).

4. Induction of Early Necrosis in SaS

The antitumour activity of vascular targeting agents is manifested as an early induction of tumour necrosis. SaS-bearing mice (tumour mean geometric diameter around 6mm) were treated i.p.with combretastatin A4 phosphate, the compound of Example 2 or no drug (controls) and tumors excised 24 h later. After fixation in formalin, sections were made from paraffin-embedded tumors and stained with

hematoxylin and eosin. Sections were scored under the microscope in a blinded fashion according to the following scale: 0-10% necrosis = 1, 11-20% necrosis = 2, and so on until 91-100% necrosis =10. Results are mean scores of sections from at least three tumours. In this assay combretastatin A4 phosphate had little or no activity but the compound of Example 2, even when administered at a lower dose, had marked activity (Table 1).

Table 1. Induction of Necrosis in the SaS tumour

Drug (dose)	Mean Necrosis Score±SEM
Control	1.0 ± 0.0
CA4P (500mg/kg)	1.3 ± 0.2
Compound of Example 2 (300mg/kg)	7.2 ± 0.2

5. Growth Delay

Tumor growth was measured following i.p. dose administration. Tumor dimensions were measured in 3 orthogonal diameters using calipers. Five mice were included per treatment group. Growth delay was determined by the time taken to grow to 9 mm (geometric mean diameter, approximately 3mm diameter increase from starting diameter) minus the time for controls to do the same. In this assay combretastatin A4 phosphate (150mg/kg, i.p.) induced growth delay of 0.0 days whereas the compound of Example 2 (150mg/kg, i.p.) induced growth delay of 3.0days.

6. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity or the application of any patent issued thereon.

Date: 17th August 2004

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University of California, Irvine *1980 - 1982*

POSTDOCTORAL RESEARCH INTO SYNTHESIS OF TAXANES.

EXPERIENCE

Roche Products, UK *1982 - 1991*

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Celltech plc, UK *1991-1998*

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Angiogene Pharmaceuticals Ltd, UK *1998-present*

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PROFESSIONAL QUALIFICATIONS

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PUBLICATIONS

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